AlzPED: A New Resource to Improve the Predictive Power and Translatability of Preclinical Therapeutic Research in Alzheimer's Disease Animal Models

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BACKGROUND

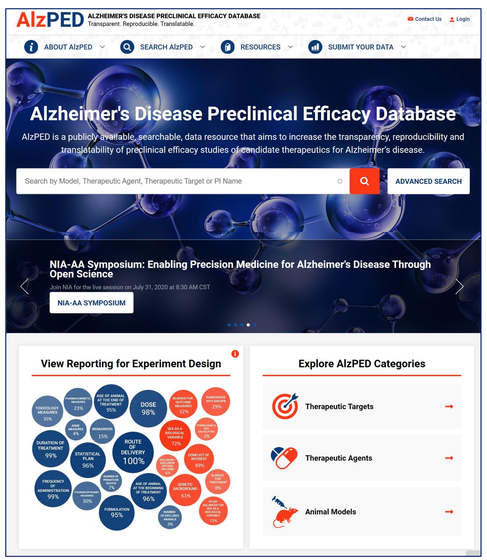
Key Factors Contributing to Poor Translation of Drug Trials in AD Animal Models to the Clinic:

- Poor rigor in study design and methodology
- Poor reproducibility of published data
- Publication bias in favor of reporting positive findings and under reporting negative findings

NIH AD Summits in 2012 & 2015

Recommendations Aimed at Increasing Predictive Power of Preclinical Testing in AD Animal Models:

1. House experimental details relating to the preclinical testing of candidate therapeutic agents in AD animal models.
2. Identify critical elements of design and methodology missing from studies.
3. House experimental details of positive and negative data to overcome publication bias.



SCOPE AND CAPABILITIES

AlzPED has the following capabilities:

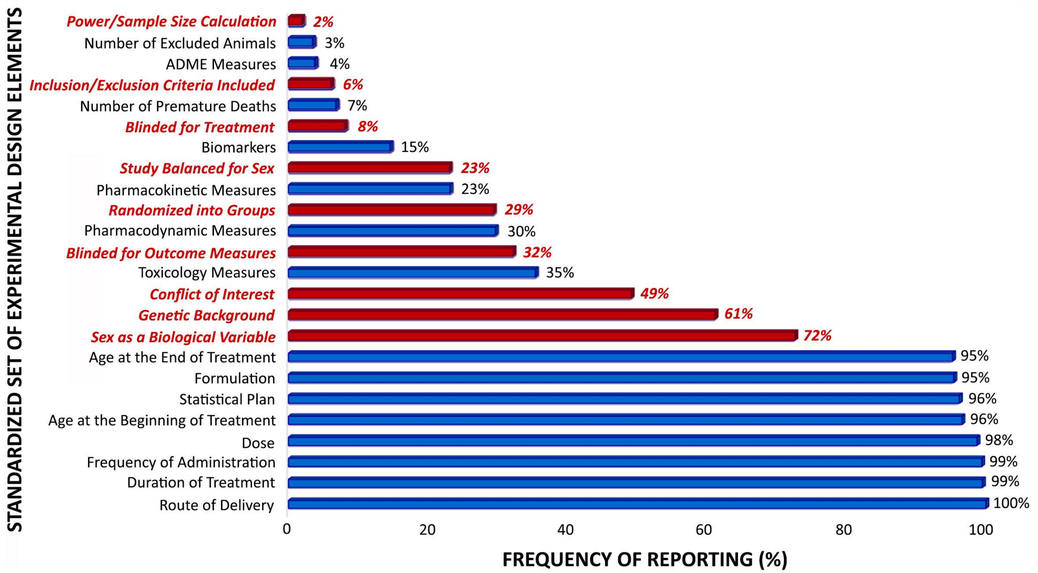
- Provide researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the **elements of rigorous study design** and **requirements for transparent reporting** – hosts curated summaries **1030** preclinical efficacy studies published between 1996 and 2019
- Influence the development and implementation of reproducibility strategies including guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics
- Provide search capability across relevant translational criteria data sets and external databases:
  - Therapy Type (**14 Therapy Types**)
  - Therapeutic Agent (**890 Therapeutic Agents**)
  - Therapeutic Target (**173 Therapeutic Targets**)
  - Animal Model (**188 Animal Models**)
  - Principal Investigator
  - Funding Source
  - Related Publications (PubMed)
  - Therapeutic Agents (PubChem and DrugBank)
  - Therapeutic Targets (Open Targets and Pharos)
  - Animal Model (Alzforum)
  - Related Clinical Trials (ClinicalTrials.gov)
  - Related Patents (Google Patents and USTPO)
- Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design
- Provide a platform for creating **citable reports/preprints** of **unpublished studies**, including studies with **negative data**
- **Report on the rigor of each study by summarizing the elements of experimental design**

CRITICAL ELEMENTS OF EXPERIMENTAL DESIGN ARE SIGNIFICANTLY UNDER-REPORTED

Experimental Design *Rigor Report Card*

Is the following information reported in the study?:

✓ Power/Sample Size Calculation	✓ Randomized into Groups
✓ Blinded for Treatment	✓ Blinded for Outcome Measures
✗ Pharmacokinetic Measures	✗ Pharmacodynamic Measures
✗ Toxicology Measures	✗ ADME Measures
✗ Biomarkers	✓ Dose
✓ Formulation	✓ Route of Delivery
✓ Duration of Treatment	✓ Frequency of Administration
✓ Age of Animal at the Beginning of Treatment	✓ Age of Animal at the End of Treatment
✓ Sex as a Biological Variable	✓ Study Balanced for Sex as a Biological Variable
✗ Number of Premature Deaths	✓ Number of Excluded Animals
✓ Statistical Plan	✓ Genetic Background
✓ Inclusion/Exclusion Criteria Included	✓ Conflict of Interest



Left: AlzPED is designed to monitor the scientific rigor of curated studies with a **"Rigor Report Card"** consisting of a standardized set of 24 experimental design elements recommended by expert advisory groups. **Right:** Graph shows the percentage of studies reporting the standardized set of 24 experimental design elements. **The red bars represent the 9 core design elements critical for scientific rigor, and reproducibility**. Data is presented as percentage reported, calculated from 1030 published preclinical studies curated to AlzPED.

CONCLUSIONS

- Analysis of more than 1000 curated studies demonstrates serious deficiencies in reporting critical elements of study design and methodology which diminish the scientific rigor, reproducibility and predictive value of preclinical therapeutic studies done in AD animal models.
- Adoption of a standardized set of best practices is very likely to improve the predictive validity of preclinical studies done in AD animal models. This measure is likely to promote the effective translation of preclinical drug testing data to the clinic.
- Journals should require investigators to follow these best practices and study design guidelines to ensure that the studies they publish are sufficiently rigorous, transparent and reproducible.
- Funding agencies should require grantees to use accepted best practices and study design guidelines to ensure that the research they fund is both rigorous, transparent and reproducible.

Detailed Analytics Summary is available here:

AlzPED Analytics